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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,852	11/04/2003	Susumu Hirose	244855US0	5771
22850	7590	04/06/2006	EXAMINER	
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			KAUSHAL, SUMESH	
			ART UNIT	PAPER NUMBER
			1633	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/699,852

Applicant(s)

HIROSE ET AL.

Examiner

Sumesh Kaushal Ph.D.

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response filed on 01/20/06 has been acknowledged.

Claims 1-6 are pending and are examined in this office action.

Claim Rejections - 35 USC § 103

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siden et al, Methods. 17(2):112-124, 1999) in view of Saffrin et al (US 4,868,311, 1989) and Chevalier et al (J Histochem. Cytochem. 45(4):481-91, 1997), for the same reasons of record as set forth in the office action mailed on 10/20/05.

Invention is drawn to a method for detecting negatively supercoiled DNA in a cell using a biotinylated psoralen probe.

Siden et al teaches use of psoralen cross-linking as probe of torsional tension and topological domain size in vivo. The cited art further teaches a protocol for measuring super-coiled DNA by treating cells with 313nm UV light and Me3-psoralen (page 116 col.2, table-1). The cited art further teaches that the binding constant intercalating agents such as psoralen and ethidium bromide are proportional to the level of negative supercoiling and there exists a linear correlation between photobinding of psoralen and negative superhelical density. The cited art further teaches that to determine superhelical density in-vivo, measurement of psoralen binding to DNA can be achieved by quantitating the incorporation psoralen into total genomic DNA (page 113, col.2, para.2-3). The cited art further teaches measurement of topological domain size by measuring R1/N values (page 114, col.1 para. 2-3; page 122, fig-3). Even though Siden teaches use of Me3-psoralen for the quantitation of super coiled DNA the cited art does not teach the use of biotinylated psoralen.

Saffrin et al teaches biotinylated-psoralen (BPsor) which cross-links to DNA in the presence of UV rays (col. 9, lines 45-55). The cited art further teaches that BPsor binds covalently to DNA in a near UV photoreaction, resulting

Art Unit: 1633

in interstrand crosslinks, and like other biotinylated molecules it binds to avidin, even after it has been incorporated into DNA. The cited art further teaches that the biotinylation does not interfere with its biological activity in lymphocytes. The cited art further teaches that the delivery of BPsor to cells as an avidin-BPsor conjugate (col. 5 lines 12-34; col.12 lines 24-68). The cited art further teaches the detection of cross-linked DNA using biotin-avidin based ELISA system (col.11 lines 23-51).

Chevalier et al provides a review for in situ hybridization (ISH) techniques using biotinylated probes. The cited art further teaches that biotin, a small vitamin molecule (M_r 244), binds with high affinity to avidin, a protein largely distributed in egg whites (M_r 70,000), which can be conjugated to different markers such as fluorescent dyes, peroxidase, ferritin, and colloidal gold (page 482, col.1 para.3). The cited are further teaches permeabilization of cells or tissue section using permeation-promoting agent (page 484, col.1 para.2; page 488, col.1 para. 4). The cited art further teaches the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Siden by substituting the Me3-psoralen with biotinlayted-psoralen (BPsor) for in situ detection of DNA. One would have been motivated to do so because biotin-avidin system provides flexibility in the selection of different diagnostic labels. One would have a reasonable expectation of success, since the use of biotin-avidin system for intra cellular detection of target moieties has been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments

The applicant arguments regarding prior issue on pages 6-7 of response filed on 1/20/06 has been fully considered. The applicant argues that Siden et al describes use of 4,5',8-trimethylpsoralen which is of smaller molecular weight as compared to biotinylated psoralan. The applicant argues that since molecular size is a major

Art Unit: 1633

determinant of biological activity, one would not expect that biotinylated psoralen would function in cells in the same way as the trimethylpsoralen described by Sinden et al. The applicant argues that for that reason, one would not have a reasonable expectation that biotinylated psoralen would interact with negatively supercoiled DNA in cells in the same way as trimethylpsoralen. The applicant argues that in view of the foregoing, the combination of Sinden et al., Saffrin et al. and Chevalier et al. fails to suggest the claimed methods.

However, applicant's arguments are found not persuasive. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case combined teaching of Sinden et al., Saffrin et al. and Chevalier et al. clearly suggest the invention as claimed, since it obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Siden by substituting the Me3-psoralen with biotinlayted-psoralen (BPsor) for in situ detection of DNA. Furthermore, one would have a reasonable expectation of success because the use of biotin-avidin system for intra cellular detection of target moieties has been routine in the art at time the instant invention was made. Chevalier et al clearly provides an over all review of an in situ hybridization (ISH) techniques, suggesting that biotin-avidin conjugate can be used for the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6). In addition Chevalier teaches the use of permeabilization of cells or tissue section using permeation-promoting agent, which further facilitate the use of biotin-avidin probes. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be

Art Unit: 1633

expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (**See MPEP 2144**). Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547**. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**



**SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633**